Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement

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ABSTRACT

- Vitamin D deficiency has re-emerged as a significant paediatric health issue, with complications including hypocalcaemic seizures, rickets, limb pain and fracture.
- A major risk factor for infants is maternal vitamin D deficiency. For older infants and children, risk factors include dark skin colour, cultural practices, prolonged breastfeeding, restricted sun exposure and certain medical conditions.
- To prevent vitamin D deficiency in infants, pregnant women, especially those who are dark-skinned or veiled, should be screened and treated for vitamin D deficiency, and breastfed infants of dark-skinned or veiled women should be supplemented with vitamin D for the first 12 months of life.
- Regular sunlight exposure can prevent vitamin D deficiency, but the safe exposure time for children is unknown.
- To prevent vitamin D deficiency, at-risk children should receive 400 IU vitamin D daily; if compliance is poor, an annual dose of 150 000 IU may be considered.
- Treatment of vitamin D deficiency involves giving ergocalciferol or cholecalciferol for 3 months (1000 IU/day if < 1 month of age; 3000 IU/day if 1–12 months of age; 5000 IU/day if > 12 months of age).
- High-dose bolus therapy (300 000–500 000 IU) should be considered for children over 12 months of age if compliance or absorption issues are suspected.

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Vitamin D deficiency and nutritional rickets are again emerging as major paediatric health issues in Australia and New Zealand.[1-5] The major cause is reduced synthesis of vitamin D_3, with dark-skinned individuals or those who remain covered when outdoors for cultural reasons being most at risk. In this consensus statement, we review vitamin D metabolism and the risk factors for, and features of, vitamin D deficiency in infants, children and adolescents, and provide recommendations for treatment and subsequent prophylaxis.

Vitamin D and metabolites

"Vitamin D" (calciferol) refers to both cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is produced by the action of ultraviolet B light (UVB; wavelength, 290–320 nm) on 7-dehydrocholesterol in the skin of humans, and is the form of vitamin D found in oily fish. Ergocalciferol is formed when ultraviolet (UV) light irradiates the fungal steroid, ergosterol. Very little ergocalciferol is available naturally in food, but it is the most readily available supplemental vitamin D. Once made in the skin or ingested, vitamin D is transported to the liver where it is hydroxylated into 25-hydroxyvitamin D (25-OHD, or calcidiol), the major circulating form of vitamin D. The concentration of 25-OHD in the serum reflects total body stores of vitamin D, and is used to assess vitamin D status. In the kidney, 25-OHD is hydroxylated to produce the biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25-$[OH]_2$D, or calcitriol). The actions of 1,25-$(OH)_2$D are to: (i) enhance absorption of calcium and phosphate from the small intestine; (ii) modify serum calcium concentration, both directly and through parathyroid hormone; and (iii) promote skeletal mineralisation.[6]

Vitamin D sources in Australia and New Zealand

Sunlight

The major source of vitamin D (more than 80%) in Australia and New Zealand is skin exposure to sunlight (UVB radiation).[7] Sun exposure also causes 99% of non-melanoma skin cancers and 95% of melanoma in Australia.[8] Thus, a balance needs to be struck between sufficient sun exposure to maintain adequate vitamin D_3 production and minimising the risk of skin cancer. No Australian or New Zealand paediatric data are available on the duration of UVB radiation exposure required to maintain adequate levels of vitamin D. Despite this, a recent Australian position statement on the risks and benefits of sun exposure advised that babies would receive enough UVB to maintain healthy vitamin D concentrations, even using sun protection, if small amounts of skin were exposed to sunlight for very brief periods before 10:00 and after 16:00 hours.[9] Adult data on the duration of sun exposure to hands, arms and face and vitamin D_3 production have recently been published.[10] Given the different body proportions of children and the reduced capacity to synthesise vitamin D with ageing,[11] children would likely require less sun exposure to produce an equivalent amount of vitamin D_3 to that of adults. Further, those at greatest risk of vitamin D deficiency in our community — individuals with increased skin pigment — may require up to six times the sun exposure to achieve the same increase in vitamin D concentrations as individuals with light-coloured skin.[12] Glass and sunscreen absorb UVB radiation, which decreases vitamin D_3 production,[13] and may increase the likelihood of vitamin D deficiency,[14] especially in individuals with pigmented skin.

Diet

An infant's vitamin D concentration reflects that of the mother.[15] If a mother is vitamin D replete, her infant has an 8–12 week store of vitamin D.[15] Human milk from vitamin D replete women has a vitamin D concentration of only 25 IU (< 1 μg) per litre.[16,17] Most commercial baby formulas in Australia and New Zealand contain 400 IU (10 μg) of vitamin D_3 per litre. An intake of 500 mL of baby formula per day therefore provides 200 IU (5 μg) of vitamin D, which is the amount recommended by the American Academy of Pediatrics as an adequate intake for healthy infants and children.[18] Milk supplemented with vitamin D_3 (up to 200 IU per 250 mL) has

recently become available. However, the average daily intake of vitamin D by Australian adults from sources such as oily fish, eggs, and butter or margarine remains at only 50–100 IU (1.2–2.6 μg).[7] So, without adequate sun exposure, consumption of vitamin D-fortified milk or vitamin D supplementation, it is difficult for pregnant and lactating mothers, breastfed babies, or children to obtain an adequate daily vitamin D intake from diet alone.

Definitions of vitamin D deficiency

Serum 25-OHD concentration provides the best indicator of vitamin D status, and should be used when testing for deficiency states (normal concentration, > 50 nmol/L).[10] The concentration of 1,25-$(OH)_2$D must not be used, as it may be elevated even in severe vitamin D deficiency. Different 25-OHD assays give different results, with some not determining 25-OHD_2 (ergocalciferol) as well as they do 25-OHD_3 (cholecalciferol).[19] This may result in spuriously reduced 25-OHD results in children supplemented with ergocalciferol.

Mild vitamin D deficiency: Serum 25-OHD concentration of 25–50 nmol/L. Serum levels over 50 nmol/L prevent secondary hyperparathyroidism[14,20] and elevated alkaline phosphatase levels.[21,22]

Moderate vitamin D deficiency: Serum 25-OHD concentration of 12.5–25 nmol/L. The incidence of hypocalcaemia and rickets increases with moderate deficiency.[3]

Severe vitamin D deficiency: Serum 25-OHD concentration less than 12.5 nmol/L. Vitamin D concentrations less than 12.5 nmol/L are seen in over 70% of children with rickets and over 90% of children with hypocalcaemia.[3]

Vitamin D is a potent steroid hormone that may have important physiological actions outside mineral homeostasis, including the regulation of cell differentiation and proliferation and immune function.[23,24] Therefore, defining vitamin D sufficiency on the basis of calcium homeostasis and bone turnover alone may not reflect all its potential actions.

Infants and children at risk of vitamin D deficiency

Current Australian and New Zealand Paediatric Surveillance Unit (APSU and NZPSU) surveys examining the incidence of and risk factors for vitamin D-deficiency rickets will improve our understanding of paediatric vitamin D deficiency. From the current data, risk factors associated with vitamin D deficiency in infants and children can be broken down into three broad areas (Box 1).[1-3,5,10,21,25,26] It is likely that multiple factors apply in a single affected individual. For example, recent migrants with a refugee background from Africa and the Middle East are at risk of vitamin D deficiency because of their dark skin, poor nutrition, reduced sunlight exposure and the prolonged breastfeeding of infants.

Features of vitamin D deficiency

Vitamin D deficiency has both osseous and non-osseous sequelae (Box 2). The most recognised are the osseous complications of rickets and osteomalacia. Rickets results from poor osteoid mineralisation adjacent to the growth plate, and osteomalacia from inadequate osteoid mineralisation at sites of bone modelling and remodelling.[27] While rickets is only seen during growth, with a peak incidence during the periods of rapid growth in early infancy and early puberty,[27] osteomalacia is common to both children and adults.

1 Causes of vitamin D deficiency in children and adolescents

- Reduced intake or synthesis of vitamin D_3
  - ➢ Being born to a vitamin D-deficient mother; most commonly veiled or dark-skinned women, or women of Asian background who actively avoid exposure to sunlight
  - ➢ Prolonged breastfeeding
  - ➢ Dark skin colour
  - ➢ Reduced sun exposure — veiled or modest clothing, chronic illness or hospitalisation, intellectual disability, and excessive use of sunscreen
  - ➢ Low intake of foods containing vitamin D
- Abnormal gut function or malabsorption
  - ➢ Small-bowel disorders (eg, coeliac disease)
  - ➢ Pancreatic insufficiency (eg, cystic fibrosis)
  - ➢ Biliary obstruction (eg, biliary atresia)
- Reduced synthesis or increased degradation of 25-OHD or 1,25-$(OH)_2$D
  - ➢ Chronic liver or renal disease
  - ➢ Drugs: rifampicin, isoniazid and anticonvulsants

25-OHD = 25-hydroxyvitamin D or calcidiol.
1,25-$(OH)_2$D = 1,25-dihydroxyvitamin D or calcitriol. ◆

2 Osseous signs of vitamin D deficiency (common to less common)

- Swelling of wrists and ankles
- Rachitic rosary (enlarged costochondral joints felt lateral to the nipple line)
- Genu varum, genu valgum or windswept deformities of the knee
- Frontal bossing
- Limb pain and fracture
- Craniotabes (softening of skull bones, usually evident on palpation of cranial sutures in the first 3 months)
- Hypocalcaemia — seizures, carpopedal spasm
- Myopathy, delayed motor development
- Delayed fontanelle closure
- Delayed tooth eruption
- Enamel hypoplasia
- Raised intracranial pressure
- Brown tumour secondary hyperparathyroidism

Radiological features

- ➢ Cupping, splaying and fraying of the metaphysis of the ulna, radius and costochondral junction
- ➢ Coarse trabecular pattern of metaphysis
- ➢ Osteopenia
- ➢ Fractures ◆

Non-osseous features of vitamin D deficiency include dilated cardiomegaly[28] and marrow fibrosis with pancytopenia or microcytic hypochromic anaemia. Note the co-existence of vitamin D deficiency and iron deficiency.[3] Other possible associations include disregulation of immune function and cellular differentiation and proliferation, and type 1 diabetes.[23,24,29]

Biochemical features of vitamin D deficiency

Vitamin D deficiency results in hypocalcaemia, secondary hyperparathyroidism, hypophosphataemia and elevated alkaline phosphatase titres.[3] Many variations on this pattern may be observed,

3 Management of vitamin D deficiency

Age	Hypocalcaemia*		Vitamin D deficiency†		Monitoring
	Seizure	No seizure	Acute	Maintenance	
< 1 month 1–12 months > 12 months	10% calcium gluconate: 0.5 mL/kg (max 20 mL) intravenously over 30–60 minutes.	Calcium: 40–80 mg/kg/day (1–2 mmol/kg/day) orally in 4–6 doses, and Calcitriol: 50–100 ng/kg/day orally in 2–3 doses until serum calcium level is > 2.1 mmol/L.	Vitamin D: 1000 IU (25 μg) daily for 3 months. Vitamin D: 3000 IU (75 μg) daily for 3 months, or 300 000 IU (7500 μg) over 1–7 days. Vitamin D: 5000 IU (125 μg) daily for 3 months, or 500 000 IU (15 000 μg) over 1–7 days.	Vitamin D: 400 IU (10 μg) daily or 150 000 IU (3750 μg) at the start of autumn.‡	**1 month:** Serum calcium and alkaline phosphatase. **3 months:** Serum calcium, magnesium, phosphate, alkaline phosphatase, calcidiol, parathyroid hormone. Wrist x-ray to assess healing of rickets. **Annual:** Calcidiol.

* Aim of therapy is to stop seizure activity, not to normalise serum calcium.[27] If seizures persist, a repeat bolus should be given and a calcium infusion of up to 4 mmol/kg/day may be required to maintain normocalcaemia. Calcium may be used intravenously to treat hypocalcaemia in the absence of seizures, but the risk of calcium burns and scarring must be considered. 1α-hydroxyvitamin D_3 is an alternative to calcitriol at 60–120 ng/kg/day. † Ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3). ‡ This is high-dose vitamin D therapy (stoss therapy), and hypercalcaemia and nephrocalcinosis have been reported with such therapy in well nourished children.[31]
Calcitriol = 1,25-dihydroxyvitamin D. Calcidiol = 25-hydroxyvitamin D. ◆

4 Recommended daily intake of calcium for healthy children[33]

Age	Adequate intake of calcium (mg/day)
0–6 months	210
6–12 months	270
1–3 years	500
4–8 years	800
9–18 years	1300

with elevated alkaline phosphatase titres being seen most commonly. Not infrequently, infants with profound hypocalcaemia and secondary hyperparathyroidism have normal or elevated serum phosphate levels, which may represent parathyroid hormone resistance at both the bone and renal level from prolonged vitamin D deficiency.[3,30] This can lead to confusion with hypoparathyroidism or pseudohypoparathyroidism, as serum calcium and phosphate concentration results are frequently available before those for vitamin D and parathyroid hormone (PTH).[3] Concentrations of calcitriol (1,25-$[OH]_2$D) may be low, normal or high at the time of diagnosis, and are of no value in making the diagnosis.

Recommendations for treating moderate to severe vitamin D deficiency

Both ergocalciferol (25-OHD_2) and cholecalciferol (25-OHD_3) are effective therapy for vitamin D deficiency, with ergocalciferol being the most widely available preparation (Box 3). Replenishment of vitamin D stores requires a total vitamin D dose of 100 000–500 000 IU, depending on age (Box 3).[32] Treatment with calcitriol (1,25-$[OH]_2$D) is only indicated for hypocalcaemia (see below). Calcium supplementation is recommended if dietary intake is poor (Box 4). It should be noted that dietary calcium deficiency is a major risk factor for the development of rickets in Africa, and should be considered in the migrant population.[31] If vitamin D deficiency or rickets does not resolve after adequate treatment, the child should be investigated for a malabsorption disorder (eg, coeliac disease) or a genetic rachitic disorder (eg, X-linked hypophosphataemic rickets).

The most serious consequence of vitamin D deficiency is hypocalcaemic seizure. While most common in infants aged less than 6 months, seizures can occur at any age. Bolus intravenous calcium is indicated to treat seizures and carpopedal spasm. A calcium infusion may be required if control is not achieved with 1 to 2 bolus doses (Box 3). Care must be taken when administering calcium intravenously, as extravasation results in severe chemical burns to the skin and subcutaneous tissues. Although it may be argued that 1,25-$(OH)_2$D production after administration of 25-OHD would be sufficient to reverse hypocalcaemia, it is our opinion that either calcitriol or 1α-hydroxyvitamin D_3 be coadministered until the serum calcium concentration is within normal limits. Children should be kept under close observation until the serum calcium concentration is over 1.8 mmol/L.

While vitamin D deficiency is the most common cause of hypocalcaemia after the first 4 days of life, other causes include dietary phosphate load, hypomagnesaemia, transient hypoparathyroidism, transient PTH resistance and congenital hypoparathyroidism.[34] Levels of PTH and magnesium should therefore be assessed during the initial investigation of paediatric hypocalcaemia.

Stoss therapy

High-dose vitamin D therapy (stoss therapy) is an effective method for treating established or recalcitrant vitamin D deficiency.[31,35] It involves oral or intramuscular administration of the total treatment dose of vitamin D (cholecalciferol or ergocalciferol), 300 000 IU (7500 μg) to 500 000 IU (12 500 μg), as a single dose, or two to four divided doses.[36] The interval between doses can vary from days to several weeks

Consensus process

This consensus statement was developed by a working group which included members of the Australasian Paediatric Endocrine Group, Paediatric Bone Australasia, migrant health paediatricians, obstetricians, public health specialists and a member of the working group responsible for the adult guidelines on vitamin D and bone health. All authors had an active role in the development of the statement and agree to its recommendations. Treatment guidelines were arrived at through a combination of published best practice and local experience. ◆

depending on the protocol followed. There are many stoss therapy regimens, and further study is required to finalise the most effective regimen and ensure safety. After stoss therapy, the biochemical follow-up recommended is similar to that for daily dosing.

In Australia, concentrated vitamin D is not commercially available, limiting stoss therapy. In New Zealand, Calciferol Strong (50 000 IU cholecalciferol; PSM Healthcare, Auckland, NZ) — an oral preparation — is available.[10] High-dose vitamin D for intramuscular injection effectively treats vitamin D deficiency secondary to malabsorption,[35] but is not available in Australia or New Zealand. To facilitate the use of stoss therapy, a wider variety of vitamin D preparations are required in Australia and New Zealand.

Prevention of vitamin D deficiency

Infants (< 12 months)

The most important factor for the development of vitamin D deficiency in infants is maternal vitamin D status.[26,27] All pregnant women, especially those who are veiled or dark-skinned, should have their serum 25-OHD concentration evaluated during the first trimester of pregnancy. If they are moderately to severely vitamin D deficient, pregnant women should be treated with 3000–5000 IU daily until the serum 25-OHD concentration is over 50 nmol/L.[10] These preparations should not contain vitamin A, which may lead to fetal toxicity. After this serum concentration is achieved, they should receive 400 IU daily, as should women with a mild deficiency.[10,37] Routine vitamin D supplementation of all pregnant women is a controversial subject,[37,38] and until local data are available on the incidence of vitamin D deficiency, this cannot be recommended.

We endorse breastfeeding for all infants. However, breast milk is a poor source of vitamin D.[16,17] The American Academy of Pediatrics recommends supplementing all breastfed infants with vitamin D until they are weaned to 500 mL per day of vitamin D-fortified formula.[18] While similar recommendations cannot be made in Australia and New Zealand until data are available on the vitamin D status of "low-risk" infants,[26] breastfed infants of veiled or dark-skinned mothers should be supplemented with 400 IU vitamin D daily (eg, 0.45 mL Pentavite; Roche Consumer Health, Sydney, NSW) until at least 12 months of age.[31] Other vitamin D preparations may be available at hospital pharmacies.

Toddlers and adolescents

While most healthy children in Australia and New Zealand receive enough sunlight exposure to maintain adequate vitamin D levels, a significant number living in the more temperate zones develop mild vitamin D deficiency during winter.[21] In Tasmania, 8% of 8-year-old and 68% of 16-year-old children have serum 25-OHD concentrations less than 50 nmol/L.[21,22] New Zealand data are comparable, with 50% of all children in all age groups with serum 25-OHD concentrations less than 50 nmol/L. If children can be encouraged to participate in regular outdoor activities, blanket vitamin D supplementation for children and adolescents is not warranted.

Children who are dark-skinned, veiled, exposed to reduced sunlight or who have an underlying medical condition, should receive 400 IU vitamin D daily (eg, be given a multivitamin) to prevent vitamin D deficiency.[18] Siblings of a child diagnosed with vitamin D deficiency should be screened.[3] The help of local community and cultural groups will be of major importance in ensuring the dissemination of these prevention strategies.

Competing interests

None identified.

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